

## LETTER TO THE EDITOR

# A hematologic support score for longitudinal measurement of blood and iron requirements in hereditary hemorrhagic telangiectasia and other chronic bleeding disorders

Hereditary hemorrhagic telangiectasia (HHT, Osler-Weber-Rendu disease) is a relatively common heritable bleeding disorder affecting 1 in 5000 people.<sup>1</sup> Unlike many other congenital bleeding disorders, such as hemophilia, individuals with HHT most often experience chronic gastrointestinal bleeding and epistaxis rather than acute, discrete major bleeding episodes. As a result, iron deficiency anemia is common in these individuals, and a mainstay of their care is anemia management.<sup>2</sup> As HHT is a remarkably heterogeneous disorder, severity of anemia may range from mild and easily controlled with oral iron to very severe, requiring weekly red cell transfusion and/or intravenous iron infusion to maintain a hemoglobin in the range of 6–8 g/dL.<sup>3</sup>

While there are currently no US Food and Drug Administration-approved treatments for HHT, recent breakthroughs in systemic antiangiogenic therapies such as bevacizumab, pazopanib, and pomalidomide are rapidly changing the landscape of this disease.<sup>4,5</sup> As such, prospective clinical trials of these agents have either begun or are planned to begin soon. A major challenge to studies in HHT is the lack of a simple, intuitive, validated method to quantify hematologic support requirements—namely, red cell transfusion and iron infusion—that can quantify outcomes in observational and interventional trials. As individuals with HHT often require a combination of red cell transfusion and iron infusion support, an objective quantitative metric of overall hematologic support could serve as a primary end point for many studies of HHT-associated bleeding.

Most modern pharmaceutical studies of anemia management are in sickle cell disease, thalassemia, autoimmune hemolysis, and other hemolytic anemias characterized by iron overload rather than iron deficiency, resulting in red cell transfusion as the sole relevant hematologic support modality. HHT is notably distinct from these conditions. The anemia of HHT is due to chronic blood loss and resultant iron deficiency in individuals with an otherwise normal, well-functioning bone marrow and not due to ineffective erythropoiesis or chronic red cell abnormalities. Therefore, in a chronic blood loss state such as HHT, intravenous iron infusion and red cell transfusion generally function interchangeably. While intravenous iron infusion is typically the preferred hematologic support

modality in HHT, red cell transfusions are very often needed in addition to iron infusion in more severe cases or at the time of a brisk bleed. Therefore, both red cell and iron infusion support must be assessed to obtain a clear picture of disease severity and the impact of any interventions. This necessitates two distinct end points: number of red cell units transfused and number of intravenous iron infusions (or quantity of elemental iron infused). This is evidenced in the recently published international, multicenter InHIBIT-Bleed study of systemic bevacizumab for bleeding in HHT<sup>3</sup> and the largest ongoing randomized clinical trial of antiangiogenic therapy in HHT, the multicenter PATH-HHT study.<sup>6</sup> Strikingly, although there are many other conditions outside of HHT that are also associated with chronic blood loss anemia (such as menstrual/gynecological blood loss or angiodysplasia of the intestines), these conditions also lack a well-validated or widely accepted means to quantify both red cell transfusions and intravenous iron into a single support measure.

Therefore, we propose the Hematologic Support Score (HSS) for the unified measurement of red cell transfusion and iron infusion as a single end point (Figure 1). This novel, simple, and intuitive score is applied to convert all red cell units transfused and iron infusions (which may be highly disparate in the quantity of elemental iron infused from one product or infusion to another) into a single value, a one- or two-digit number carried out to one decimal place (ie, 2.4 or 13.7). The HSS effectively converts quantities of elemental iron infused into red cell unit equivalents by taking advantage of the known quantity of elemental iron contained within a standard unit of packed red cells administered to adult patients (approximately 250 mg).<sup>7,8</sup> This method creates a standardized comparator of hematologic support needs in a single patient or between patients,

$$\text{HSS} = \text{Units RBCs Transfused} + \frac{\text{Milligrams Elemental Fe}}{250}$$

**FIGURE 1** The Hematologic Support Score (HSS). Fe, iron; RBCs, red blood cells

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**TABLE 1** Application of the HSS to a previously published cohort of patients with HHT-associated bleeding treated with systemic bevacizumab<sup>9</sup>

Patient no.	6 months before bevacizumab			6 months on bevacizumab maintenance			Change in HSS	
	RBC units	Iron infused (mg)	HSS	RBC units	Iron infused (mg)	HSS	Absolute	Relative
1	12	4590	30.4	15	1530	21.1	-9.2	-30%
2	30	2800	41.2	0	1200	4.8	-36.4	-88%
3	0	3570	14.3	0	750	3	-11.3	-79%
4	32	1600	38.4	0	0	0.0	-38.4	-100%
5	6	2040	14.2	0	510	2.0	-12.1	-86%
6	0	0	0.0	0	1020	4.1	+4.1	N/A <sup>a</sup>
7	59	5610	81.4	0	510	2.0	-79.4	-98%
8	9	1680	15.7	0	280	1.1	-14.6	-93%
9	4	6000	28.0	0	1500	6.0	-22.0	-79%
10	3	0	3.0	0	0	0.0	-3.0	-100%
11	19	2040	27.2	0	1020	4.1	-23.1	-85%
12	2	5100	22.4	0	510	2.0	-20.4	-91%
13	4	1020	8.1	0	1020	4.1	-4.0	-50%

Note: RBC transfusions and quantity of elemental iron infused in the 6 mo before treatment are compared with the first 6 mo of bevacizumab maintenance (following a 2-mo bevacizumab induction). Despite wide variations in RBCs transfused and elemental iron infusions between patients and within patients before and after treatment, the HSS gives a clear indication of severity and support requirements and allows for simple comparisons between patients and pre versus post treatment.

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; HSS, Hematologic Support Score; RBC, red blood cell.

<sup>a</sup>Relative change not calculatable due to score of 0.0 before treatment.

who may require a variable combination of red cell transfusion and iron infusions during a study period or over the course of routine clinical care.

The HSS is reported over a period of time (generally a period of months) to facilitate comparison. For example, if a patient's 3-month HSS before treatment was 6.4, and after treatment was 3.1, the difference can then be described in absolute terms (a 3.3-point reduction) or in relative terms (a 52% reduction). Should a patient have a synchronous reduction in red cell transfusion and proportional increase in iron infusions, this would be accurately reflected as an essentially unchanged HSS, whereas this would not be reflected in separate measurements of the support modalities (especially if, for example, transfusions were held up as a primary outcome and iron infusions were a secondary outcome). Table 1 demonstrates the application of the HSS in a previously published cohort of 13 individuals with HHT treated with systemic bevacizumab.<sup>9</sup>

The HSS has promise in use to define HHT bleeding severity into categories (eg, mild, moderate, severe) using specific numerical thresholds and can be used to define target populations for clinical trials based on severity. It also has the potential to be extended to clinical trials in other chronic blood loss states. Its simplicity—that it is calculated with just the two essential values of red cell units transfused and milligrams of elemental iron infused—and adaptability to any desired time period add to its strengths as a metric.

However, the HSS does have some limitations. While the score would be expected to be generally applicable in adult populations, its use in pediatric populations, which rely on weight-based transfusion regimens, would require modification (application of a coefficient to the “Units of Red Cells Transfused” portion of the equation) to remain accurate. Additionally, the HSS does not account for the contribution of oral iron, for which the amount absorbed will vary widely between individuals and formulations and is not readily measured. This can, however, be considered separately or controlled in other ways in the setting of a trial (ie, a requirement that patients on oral iron at enrollment must be continued at the same dose over the study period).

In conclusion, the HSS is a simple score to accurately combine red cell transfusion and iron infusion into a single end point. This proposed score requires use in future studies of HHT and other chronic bleeding conditions to validate it as a useful longitudinal measure of chronic bleeding.

## KEYWORDS

blood transfusion, clinical trials, hereditary hemorrhagic telangiectasia, HHT, intravenous iron, Osler-Weber-Rendu

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## AUTHOR CONTRIBUTIONS

HA-S wrote the first draft of the manuscript and contributed to concept and design, creation of the tables and figures, critical revision of the intellectual content, and final approval. RPN and NAZ contributed to critical revision of the intellectual content and final approval.

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